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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,499	02/08/2002	Neil M. Wolfman	8702.0100-00	3454

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EXAMINER	
CHAPPELL, CHERIE M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,499	WOLFMAN ET AL.	
	Examiner	Art Unit	
	Cherie M. Chappell	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-35,38,42-48,50-59,119-132,137-142 and 144-173* is/are pending in the application.

4a) Of the above claim(s) *33-35, 38, 42-48, 50-59, and 137-142* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-132 and 144-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/13/03, 11/02/04, 6/24/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

Applicant's amendments of 12 November 2004, drawn to non-elected, withdrawn claims are noted. However, no withdrawn claims are currently under examination. Claims 33-35, 38, 42-48, 50-59, 119-132, 137-142, and 144-173 are pending. The amendment dated 24 June 2005 has been entered into the record. New claims 172 and 173 have been added. Claims 119-132 and 144-173 are under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Information Disclosure Statements

1. The Information Disclosure Statement filed 13 March 2003 has been considered and a signed copy is attached. The Information Disclosure Statement filed 12 November 2004 has been considered and a signed copy is attached. The Information Disclosure Statement filed 24 June 2005 has been considered and a signed copy is attached.

2. The two International Search Reports mailed 4 February 2003 and 25 February 2003 were not considered because they are not in conformance with MPEP 609. If the individual references contained in those search reports are submitted in conformance with MPEP 609, they will be considered.

3. Journal articles by Thies *et al.*, and Zwijsen *et al.*, were improperly cited by Applicant. Both non-patent documents were considered and the correct citation placed on the attached PTO-892.

Claim Rejections - 35 USC § 112, First Paragraph - Enablement
New Rejection

4. Claims 119-132 and 144-173 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8)

quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The terms "modified" and "modifies" do not limit the possible modifications to the GDF-8 propeptide or a fragment thereof, nor do they limit the potential modifications to the aspartate residue at position 76. The skilled artisan would not be able to determine how this peptide was to be modified and thus would not be able to determine what Applicant intended this vague limitation to encompass. Further, because there are no functional limitations, apart from the inherent activities of the GDF-8 propeptide, one of skill in the art would not be able to determine the extent of modification that would be tolerated. The specification fails to provide guidance on what kinds of modifications are to be made to residues other than the aspartate residue at position 76, if any, and offer only an invitation for further experimentation (see specification p. 9, lines 22-24).

Additionally, Applicant has claimed an amino acid sequence that is at least 75% identical to SEQ ID NO: 5 (the propeptide region of human GDF-8), in claims 119-132 and 144-173. However, this fails to correlate reasonably with the disclosure set forth in the specification for the following reasons. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, cleavage, activity and in providing the correct three-dimensional spatial orientation of binding, cleavage, and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions, mutations, or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active protein fragments, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active, cleavage, or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would

immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 119-132 and 144-173 are directed to amino acid sequences that are at least 75% identical to SEQ ID NO: 5 and fragments thereof. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks *et al.* (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity.

Claim Rejections - 35 USC § 112, First Paragraph – Written Description
New Rejection

5. Claims 119-132 and 144-173 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The terms "modified" and "modifies" do not limit possible changes or alterations to the GDF-8 propeptide or a

fragment thereof, nor do they limit potential alterations to the aspartate residue at position 76. The skilled artisan would not be able to determine how this peptide or fragment is to be modified and thus would not be able to determine what Applicant intended this vague limitation to encompass. Further, because there are no functional limitations, one of skill in the art would not be able to determine the extent of modification that would be tolerated. The specification fails to adequately describe what kinds of modifications are to be made to residues other than the aspartate residue at position 76, if any, and offer only an invitation for further experimentation (see specification p. 9, lines 22-24).

Claims 119-132 and 144-173 are directed to amino acid sequences that are at least 75% identical to SEQ ID NO: 5 and fragments thereof. In the instant case, Applicant's have not adequately described what changes to make to establish 75% sequence identity with SEQ ID NO: 5 or fragments. Additionally, Applicants have not adequately described which residues are critical for function of the protein. The skilled artisan would not be able to determine the extent of modifications that would be tolerated because there are no functional limitations specified with regard to proteins that are at least 75% identical to SEQ ID NO: 5 or its fragments. The claimed subject matter must be described in the specification to ensure that applicant had in his possession, as of the filing of the application, the specific subject matter claimed. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass*, 492 F.2d 1228, 181 USQ 31 (CCPA 1974).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession f the invention. The invention is, for purpose of the 'written description' requirement, whatever is now claimed." (See p. 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See *Vas-Cath,* at 1116). As discussed above, the skilled artisan cannot envision the detailed amino acid structure of the encompassed homologous polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See, *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

35 USC § 112, Second Paragraph – Indefiniteness
Claim Objections/Rejections Withdrawn

2. Applicant's arguments, see Amendments, filed 24 June 2005, with respect to the rejection of claims 119-132 and 144-171 under 35 USC 112, second paragraph, for being indefinite in containing the term "biologically active" have been fully considered and are persuasive. The rejection of claims 119-132 and 144-171 under 35 USC 112, second paragraph, for indefiniteness as to the term "biologically active" has been withdrawn.

Claim Rejections - 35 USC § 102(a)
Claim Rejection Partially Withdrawn and Partially Maintained

3. Applicant's arguments, see Amendments, filed 24 June 2005, with respect to the rejection of claims 144-159 under 35 USC 102(a) as being anticipated by WO 200043781 for the reasons set forth in the office action of 24 January 2005, have been fully considered and are persuasive in part. Applicant's Amendments are insufficient to overcome the rejection as to claims 153-159. As written in claims 153-159, there is still no requirement in the claims that the modified GDF-8 propeptide have a mutation at position 76. That limitation refers only to the moiety of section (b) of claim 144. The rejection of claims 144-159 under 35 USC 102(a) as being anticipated by WO 200043781 for the reasons set forth in the office action of 24 January 2005, as well as for the reasons in this paragraph, is withdrawn as to claims 144-152 and is maintained as to claims 153-159.

New Claim Rejection

7. Claims 119-132 are rejected under 35 USC 102(a) as being anticipated by WO 200043781. As written, there is no requirement in the claims that the modified GDF-8 propeptide have a mutation at position 76. That limitation refers only to the moiety of section (b) of claim 119.

Claim Rejections - 35 USC § 103(a)

Claim Rejections Maintained

4. The rejection of claims 160-164 under 35 USC 103 as being unpatentable over WO 200043781 in view of US patent 5,723,125, for the reasons set forth in the office actions of 24 January 2005 and 21 August 2003, is maintained.

New Claim Rejection

Claims 119-132 and 144-173 are rejected under 35 U.S.C. 103 as being unpatentable over WO 200043781 in view of Lee *et al.* (1990 J Biol Chem 265(35):21992-21996; see the 1449 submitted 24 June 2005). WO 200043781 teaches GDF-8 from several species in figure 11. It further teaches that the propeptide region of GDF-8 is inhibitory (figures 14 and 15). WO 200043781 also teaches that peptide fragments can be derived from the pro-domain that is upstream of the 99th residue (Asp99 in figure 11) (p. 9, lines 17-18) and it teaches a preferred embodiment that includes pro-GDF-8 as an inhibitor, comprising the N-terminus of the pro-domain of GDF-8 that is upstream of the 99th residue (Asp99 in figure 11) (p. 22, lines 22-24). Moreover, variants of the proregion, including altered proteolytic sites are taught on pp. 20-21.

WO 200043781 also teaches the aspartate residue at position 99 (D99) (figure 11), corresponding to the instant SEQ ID NO: 5 aparatate residue 76 (D76), which is highly conserved and is identical in all ten species listed. WO 200043781 also teaches this highly conserved protolytic region (DDSSD) in SEQ ID NO: 27, corresponding to residues D76 to D80 of instant SEQ ID NO: 5 (p. 62, lines 19-21).

Additionally, WO 200043781 teaches cleavage site variants where "mutations in the conserved cleavage sequences, required for activation, can result in the synthesis of non-functional GDF-8 and GDF-11 molecules" (at p. 21, lines 14-15). Examples and references for preparing cleavage site mutants are also provided (p. 21, lines 21-26). Specifically, WO 200043781 teaches the polypeptide migrating at 25 kDa, a product of alternate cleavage at Arg 99 (Arg 98 according to figure 11), was inactive (p. 63, lines1-8). This indicates that the inhibitory (or GDF-binding) domain is located t the N-terminus of the pro-domain, upstream of Arg 99 (Arg 98 according to figure 11). It also teaches that GDF-8 inhibitors of small molecular size may be designed based on the sequence of the pro-domain upstream of Arg 99 (Arg 98 according to figure 11) (see also, figure 13 and p.63, lines 6-7).

WO 200043781 also teaches activities of pro-GDF-8 and variants that include interference with preadipocyte (fibroblast) differentiation to adipocytes (p. 29, lines 8-21), regulation of glucose uptake (p. 29, lines 24-31 and p. 30, lines 1-6), and inhibition of GDF-8 activities (p.33, lines 19-20).

WO 200043781 does not teach a specific mutation at the aspartate residue in instant SEQ ID NO: 5, position 76 (D76). However, the limitation of modifying D76 of instant SEQ ID NO: 5 would have been obvious to one skilled in the art over the cleavage site mutants taught by WO 200043781. Evidence of proteolytic cleavage at conserved n aspartate residues members is well known in the art.

Lee *et al.*, teach the importance of aspartate residues in rendering proteolytic sites susceptible to cleavage by C-proteinases. Lee *et al.* (1990 J Biol Chem 265(35):21992-21996; reference #62 on the 1449 submitted 24 June 2005) demonstrated an aspartate (D) to glycine (G) mutation in a highly conserved aspartate residue and determined that the conserved aspartate residue is a necessary component of the cleavage site (p. 21995, column 2, third paragraph). Further evidence is provided by Li *et al.*, (1996 Proc Nat Acad Sci USA 93:5127-5130; see the 1449 submitted 24 June 2005) who show that the pro-collagen C-proteinase, demonstrated by Lee *et al.*, is identical to bone morphogenic protein-1 (BMP-1), which is a zinc-requiring endopeptidase.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. There are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Even so, the instant case is unique because there is a naturally occurring mutation in bovines at D77 of instant SEQ ID NO. 5 (D100 of figure 11 in WO 200043781) that changes the conserved aspartate to alanine. This bovine mutation is known not to directly affect the functionality of the protein. However, mutating the aspartate residue at position 76, is apparent because WO 200043781 teaches that the cleavage site lies within this highly conserved proteolytic region (DDSSD) in SEQ ID NO: 27, corresponding to residues D76 to D80 of instant SEQ ID NO: 5 (p. 62, lines 19-21) and that GDF-8 inhibitors can be designed based on the sequence of the pro-domain upstream of Arg99 (Arg 98 in figure 11 and instant Arg75 of SEQ ID NO: 5) (WO 200043781 p. 62, lines 19-21). Mutating instant Asp76 merely amounts to a further characterization of the GDF-8 prodomain, which is adequately described in the prior art.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the present invention to mutate an amino acid in the highly conserved proteolytic region as taught by WO200043781 in order to prevent the cleavage of the GDF-8 propeptide, thereby inhibiting its negative regulatory function. A mutation at the highly conserved cleavage site would prevent the protein from being cleaved,

thereby increasing its half life. There was a reasonable expectation of success in performing the method of WO 200043781 in combination with Lee *et al.*, because recombinant techniques to mutate protein residues were well known and highly successful at the time of the present invention.

8. Claims 121-126, 129-131, and 167-170 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 200043781 in view of U.S. patent 5,723,125 (Chang et al., 1998; see the 1449 submitted 24 June 2005).

WO 200043781 teaches as set forth above but fails to teach GDF-8 proregion/IgG1 Fc or IgG4 Fc or immunoglobulin fusion proteins, as claimed in instant claims 121-126, 129-131, 161-164, and 167-170. The '125 patent teaches fusion of interferon with IgG1 or IgG4 as a means of prolonging the half life of the interferon (column 2, lines 16-59, column 5, lines 54-59). It would have been obvious to one of ordinary skill in the art to combine the teachings of WO 200043781 with the '125 patent to produce Fc fusion proteins. One of ordinary skill would have been motivated to do so because WO200043781 teaches useful protein therapeutic inhibitors of GDF-8 and the '125 patent teaches methods of improving the efficiency of protein therapeutic agents. Additionally, linker proteins function as molecular scaffolds to localize enzymes with substrates. The skilled artisan would be motivated to use linker proteins to provide stability in fusion proteins.

9. Claims 127, 129-130, and 160 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 200043781 in view of US patent 5,116,944 (Simvan *et al.*, 1992).

WO 200043781 teaches as set forth above but fails to teach GDF-8 proregion/albumin fusions, as claimed in instant claims 127, 129, 130, and 160. The '944 patent teaches methods of improving the efficiency of protein therapeutic agents, in part by fusing proteins with albumin as a means of prolonging their half lives by reducing toxicity (column 4, lines 34-49). It would have been obvious to one of ordinary skill in the art to combine the teachings of WO 200043781 with the '944 patent to produce albumin fusion proteins or associating proteins with albumin to prolong their half-lives. One of ordinary skill would have been motivated to do so because WO 200043781 teaches useful protein therapeutic inhibitors of GDF-8 and the '944 patent teaches methods of improving the efficiency of protein therapeutic agents.

10. Claims 128-130 and 160 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 200043781 in view of US patent 4,179,337 (Davis et al., 1979).

WO 200043781 teaches as set forth above but fails to teach GDF-8 proregion/polymer fusions, as claimed in instant claims 128-130. The '337 patent teaches fusion of proteins with polyethylene glycol as a means of reducing immunogenicity (column 2, lines 11-23). It would have been obvious to one of ordinary skill in the art to combine the teachings of WO 200043781 with the '337 patent to produce pegylated GDF-8 propeptides. One of ordinary skill in the art would have been motivated to do so because WO 200043781 teaches useful protein therapeutic inhibitors of GDF-8 and the '337 patent teaches methods of increasing the usefulness of therapeutic agents.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Chappell whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMC
6 September 2005

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER